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Nitroglycerine in the Management of Retained Placenta

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I. INTRODUCTION:

The third stage of labour is the time period between vaginal delivery of baby and placental separation [1].If placenta is not separated within 30 minutes then it is considered as prolonged third stage of labour because complications may arise after this time period has exceeded [2].To separate placenta, some form of active intervention is often instituted at this time.

0.1%-2% of the deliveries are Complications due to retained placenta after child birth[3].Without treatment, it results in hemorrhage which leads to maternal death. Retroplacental myometrial contractions failure leads to retained placenta[4].Common techniques in management of retained placenta are administering the oxytocin , ergometrine or prostaglandins to induce uterine contractions and followed by controlled cord traction [5].

The most commonly used substance for placental separation is oxytocin. It can be given iv or into the umbilical vein , to the retroplacental myometrium .To induce myometrial contractions and placental detachmen. According to cochrane review, the administration of dilute oxytocin to the umbilical vein appears to be effective for placental seperation[6].The WHO guidelines for treatment of retained placenta and PPH suggest the injection of saline diluted oxytocin in to the umbilical vein[7].Operative manual removal of placenta under regional or general anaesthesia is performed when placental detachment by means of oxytocin and controlled cord traction fails.

Sequential administration of oxytocin and nitroglycerin along with controlled cord traction is an alternative method for the successful delivery of retained placenta[8-10].Nitroglycerin is commonly used to induce cervicouterine relaxation in Obstetric emergencies , when it is injected intravenously[18,20-22] uterine relaxation occurs within 45-60 seconds and normally last no longer than 2 minutes[22], it can also be given sublingually[23,12].If nitroglycerin is to be effective for medical management of retained placenta it should address atleast one of the following patho physiological mechanisms .Nitroglycerin will relax local uterine muscle constriction thereby aids in placental release. Farley et al. has suggested that nitric oxide mediated contraction and relaxation of human chorionic villi along their longitudinal axis may serve as a nitroglycerin mediated mechanism for placental separation in adherent placenta[11].

Surgical management is likely to remain the mainstay of treatment where the placenta is morbidly adherent to the myometrium as the nitric acid donor drugs like nitroglycerine are ineffective to cause relaxation in morbid adherent placenta.

Recent pilot study, stated that the sequential administration of I.V oxytocin in combination with sublingual nitroglycerin found to be effective in delivery of retained placenta in the woman who were hemodynamically stable with no signs of post partum haemorrhage [12]. The GOT-IT (Glyceryl Trinitrate for Retained Placenta) trial was a large multi-centre trial that aimed to determine the clinical effectiveness and cost-effectiveness of sublingual nitroglycerin (glyceryl trinitrate) spray compared with placebo in reducing the need for MROP in women with retained placenta after vaginal delivery.

II. AIMS AND OBJECTIVES

The primary aim of the study was to determine if oxytocin in combination with nitroglycerin is effective in the management of retained placenta, when performed by inexperienced obstetricians. Secondary aims is to examine hemodynamic effects, blood loss, and side effects following sublingual administration of nitroglycerin and to identify factors that could have a negative effect on placental detachment.

III. MATERIALS AND METHODS

This was a prospective doubleblind randomised controlled study to determine the effect of nitroglycerin in the management of retained placenta.This study was carried at chalmeda Anand

Rao institute of medical sciences, karimnagar attending obstetric emergency in the department of obstetrics and gynecology among 60 patients from 2020-2021.According to study protocol, A slow push of 10 IU oxytocin was given intravenously to promote uterine contractions and placental detachment when placenta remained undelivered 30minutes after child birth then the women were asked to participate in this study.

Inclusion criteria: uncomplicated singleton pregnancy with spontaneous vertex delivery of a healthy child at term, placenta remained undelivered 40minutes after delivery.

Exclusion criteria: serious maternal medical disease, maternal age less than 18years,blood loss more than 600ml, uterine malformation,suspected placental accreta .

According to hospital protocol,In third stage of labour 5IU of oxytocin was given either intravenously or intramuscularly within 5minutes after delivery.If the placenta remained undelivered 30 minutes after child birth, a slow push of 10 IU oxytocin administered intravenously to promote uterine contractions and placental detachment.5 minutes after injection of oxytocin, controlled cord traction was performed once more to facilitate placental delivery.If the placenta remained undelivered 40 minutes after childbirth following informed consent, the women were allocated to either of the two groups

1)1mg of nitroglycerin tablets(0.5mg Two tablets) or

2)Two placebo tablets

The tablets were given sublingually approximately 50 minites after childbirth was Neither the obstetrician nor the precipitating women were aware of the agent given.5 minutes after administration of nitroglycerin or placebo tablets, gentle persistent cord traction was performed once more for a maximum duration of 5 minutes. If the placenta was delivered in the delivery room without the need of operative manual removal under either regional or general anaesthesia, the procedure was regarded as successful. Prior to the administration of nitroglycerin or placebo tablets maternal blood pressure and pulse rate were measured.These measures were repeated 5 minutes as well as 15 minutes after administration of the tablets for assessment of possible hemodynamic effects caused by nitroglycerin.In addition, total blood loss during third stage of delivery was registered.Blood loss was assessed by weight and visual estimation, and in some cases also combined with measurement of collected blood poured into a measuring jar.The women also completed a questionnaire regarding possible side effects of nitroglycerin.
In addition, medical records were routinely checked in order to identify factors that could adversely effect the outcome of the procedure.

IV. RESULTS

60 women who agreed to participate in the study,had given their informed consent.

Thereby there were 60 patients in the intention to treat group(ITT) ,who were all randomised patients and there are 60 patients in the perprotocol group (PP).These were the randomised patients who all recieved study medication i.e;30 were given 1mg nitroglycerin and 30 were given placebo tablets.The two groups were similar regarding age,parity or site of study. For the intention to treat group (ITT) in 36.4% has detachment of placenta following sublingual administration of nitroglycerin occurred when compared to placebo group,it is 23.2%.

The corresponding results for patients per protocol group (PP) were 37.3% and 20.4% respectively. After administration of tablets,a significant difference in blood pressure and pulse rate between nitroglycerin and placebo group which occurred within 5 and 15 minutes successfully. Maximum fall in blood pressure is seen within 5 minutes after giving nitroglycerin.

However, nitroglycerin received women has moderate hemodynamic changes and were not considered clinically important. The both groups are similar regarding total blood loss or blood loss more than 1000 ml.There were no significant complications due to nitroglycerin. Both groups have headache and palpitations as side-effects.However maternal side-effects were very minimal or moderate with an intensity of maximum 6 on a VAS scale from 1 to 10. Regarding frequency & intensity of side-effects both groups has no statistical difference.

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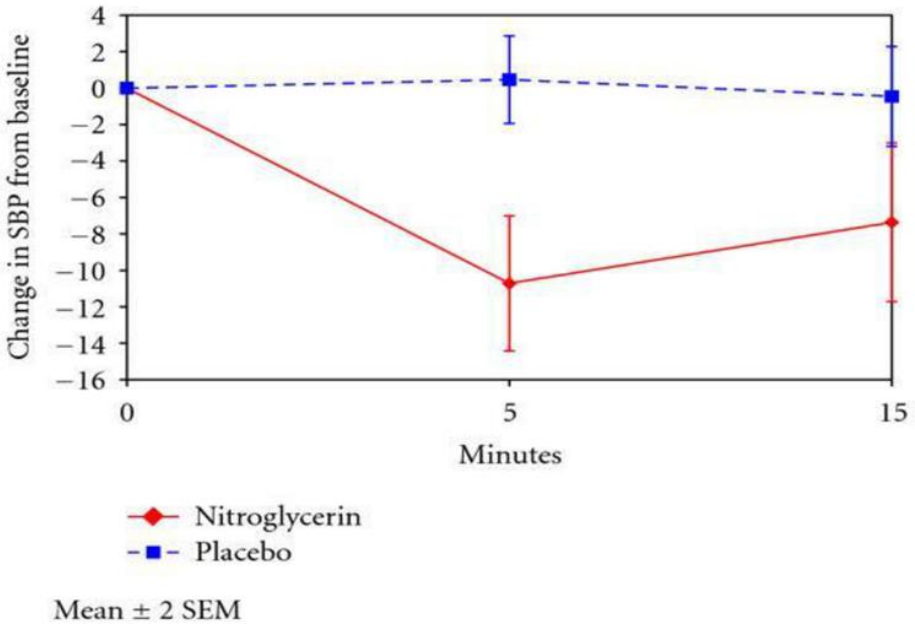
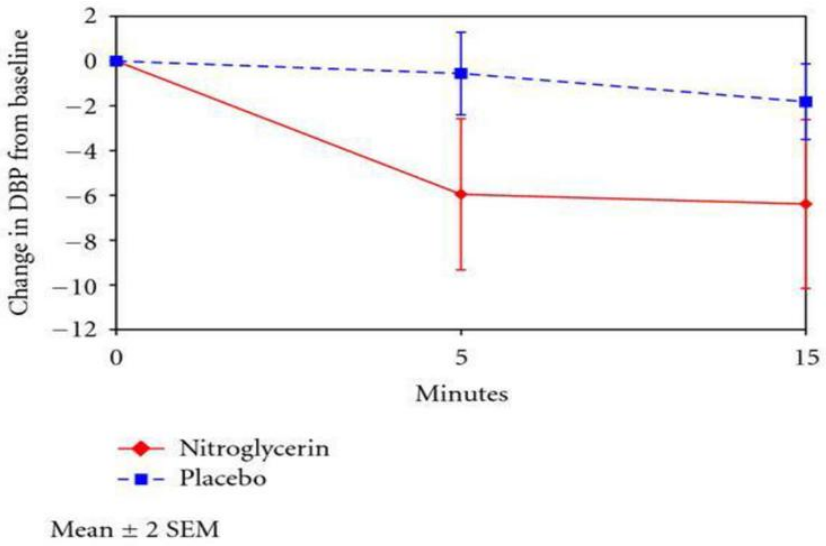
Table:1 Demographic and baseline characteristics

Variable	Nitroglycerin(n=30)	Placebo (n=30)
Age (years)		
Mean	31.7	31.7
Median (range)	32 (19; 42)	32 (20; 44)
Parity n (%)		
1	12(41.8)	13(42.9)
2	10(36.4)	11(39.3)
3	5 (18.2)	3(12.5)
4	0(0.0)	1(3.6)
5	1(3.6)	0(0.0)
Time from delivery to administration of nitroglycerin or placebo tablets (minutes)*		
Mean	**49.5**	**46.3**
Median (range)	50 (27; 70)	46 (31; 62)

Table : 2 Maternal side effects following Nitroglycerine treatment





Effect of nitroglycerine on heart rate.

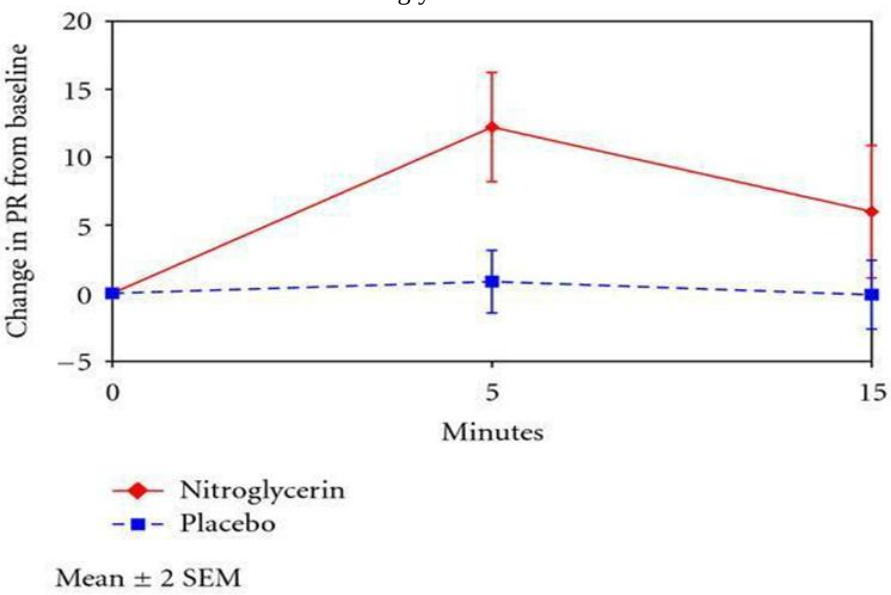


Table : 3 Maternal side effects following medical treatment (ITT)

Side effect	Nitroglycerin n = 30	Placebo n =30
Headache (VAS scale 1–10)	n = 18	n = 17
Mean	0.9	0.5
Median (range)	0.0 (0; 6)	0.0 (0; 6)

Palpitations (VAS scale 1–10)	n = 15	n = 17
Mean	0.9	0.5
Median (range)	0.0 (0; 5)	0.0 (0; 2)

Table: 4 Secondary clinical out comes after Nitroglycerine treatment

Variable	Nitroglycerine(n=30)	Placebo(n=30)
Placental detachment n(%)	11(37.3)	6(20.4)
Manual removal of placenta		
No	7(26.1)	8(27.0)
Yes	22(73.9)	21(73.0)
Total Blood loss ≥1000ml n(%)	13(43.8)	13(43.9)
More than 15% fall in Haemoglobin		
No	11(38.6)	12(42.8)
Yes	18(61.4)	17(57.2)
	26(88.6)	27(92.2)
Yes	3(11.4)	2(7.8)
Maternal Pyrexia		
No	29(97.9)	28(96.2)
Blood transfusion	1(2.1)	2(3.8)
No		
No	26(87.1)	26(87.6)
Yes	3(12.9)	3(12.4)

Statistics: A sample size containing 60 women (each group of 13) was calculated to yield a power of 90% at the 5% significance level to get 50% success rate in the treatment group while it was 20% in placebo group. Some withdrawals from the study were expected and therefore a sample size of 60 women was decided. A sample size of 60 women was decided because some withdrawls from the study were expected. Using the Mann-Whitney U test , analysis of continuous variables were made between treatment group and placebo group and chi-square test dichotomous variables.

To compare between groups , Mantel-Haenstel chi-square test and chi-square test were used for ordered categorical variables and non ordered categorical variables respectively. The confidence interval was 95% to assess the relative risk of dichotomous variables. Wilcoxon signed rank test was used to analyze the change from base line variables with in treatment groups. n(%) is for categorical variables and mean,median,min and max are of continuous variables. The significance tests were two sided and the significance level is 5%.

V. DISCUSSION:

In this study the successful release of placenta seen in 37.3%women with retained placenta after sequential administration of nitroglycerine and oxytocin. Several studies have shown the uses of nitroglycerine for release of retained placenta[13,14-17]. One randomized study examined the efficiency of sequential IV oxytocin administration and

nitroglycerine tablets administration[18] . In this study placenta is retained is successfully released in 11 women, compared to only 6 women in placebo group[13].

There are three main causes of retained placenta.
They are

I. Placenta adherens : 81%
II. Trapped placenta : 13% III. Placenta accrete : 6% [19]

Insufficient myometrial contractions leads to placenta adherens[3]. Trapped placenta is a detached placenta that is trapped behind uterine cervix. Firm attachment to myometrium leads to placenta accrete. In this study , USG is not performed to differentiate the retained placentas[19]. On Nitroglycerin administration :systolic and diastolic blood pressure decreases and pulse increase, but heamodynamic effects are transient and uterine relaxation didn't cause vaginal bleeding. Most of the women had side effects like headache and palpitations. Most of these are due to prior information about the adverse effects of nitroglycerin.

Sequential treatment with oxytocin and Nitroglycerin is to initiate uterine contraction followed by transient relaxation,thus promoting placenta detachment.In this study, negative factors could be possible 3rd stage was continued after administration of nitroglycerin.

1.oxytocin infusion in the above factors interfere with relaxative effecfs of nitroglycerin
2.continued nipple stimulation by breastfeeding the infant after nitroglycerin administration.
3.promoting contractions by uterine massage after nitroglycerin administration.[12,13]

VI. CONCLUSION

Oxytocin and nitroglycerin when administered shows an increased release of retained placenta when compared to oxytocin and placebo. However, statistical significance is not obtained when the difference in success rate is calculated. It was registered that the removal of placenta has an importance if the method is experienced clinically. There are no adverse effects of clinical significance due to nitroglycerin.

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